PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:
Liu *et al.*

APPLICATION NO.: 10/825,457

FILED: April 14, 2004

FOR: **METHOD OF TREATMENT USING INTERFERON-TAU**

EXAMINER: Dang, I.

ART UNIT: 1647

CONF. NO: 8343

DECLARATION OF DR. CHIH-PING LIU
UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Chih-Ping Liu, declare:

1. I currently serve as Chief Scientific Officer of Pepgen Corporation. Prior to serving as the Chief Scientific Officer, I was Founder and Chief Executive Officer of Pepgen Corporation, from about 1992-2003.

2. I received my Ph.D. from the University of Wisconsin-Madison, in 1977 in Genetics. I held post-doctoral positions at Yale University and at University of California Berkeley.

3. Since founding Pepgen Corporation, and particularly since the late 1990's, I have been involved in the development of interferon-tau as a pharmaceutical agent for treatment of multiple sclerosis (MS).

4. I am a named inventor on the instant application. In addition, Pepgen Corporation is the assignee of interest of the instant application.

5. In my role as Chief Scientific Office of Pepgen Corporation, I am actively involved in the clinical studies to evaluate the safety and efficacy of orally administered interferon-tau on the symptoms and disease state of persons previously diagnosed with multiple sclerosis. I supervised, or participated in, and/or have firsthand knowledge of the studies described herein.

6. A Phase I clinical study to evaluate the safety and efficacy of interferon-tau in multiple sclerosis patients has been conducted. In this study, twenty-three patients in an active disease state were selected for participation, of whom sixteen were evaluable at the six month time point of the study.

7. In the patients enrolled in the study, their disease status was classified as active based on the presence of a gadolinium-enhancing lesion observed in at least one of three magnetic resonance imaging (MRI) brain scans taken during a three month period prior to enrollment and treatment.

8. Also during the three month period prior to enrollment and treatment, blood samples were taken and the serum levels of interleukin-10 and interferon-gamma were analyzed.

9. The sixteen patients selected for the study received, via oral administration, 3.0 mg of interferon-tau three times per day, for a total daily dose of 9.0 mg. Based on a specific antiviral activity of 1-2 x 10^8 Units/mg protein, measured in a standard assay, the daily dosage given to each patient was between approximately 9 x 10^8 and 1.2 x 10^9 Units.

10. For a six month period following initiation of treatment, blood samples were taken for analysis of interleukin-10 and interferon-gamma, and MRI brain scans of each patient were taken to evaluate the number of new gadolinium-enhancing lesions.

11. MRI scans of the brain after administration of gadolinium are used to assist in the diagnosis of multiple sclerosis, to monitor the status and progression of the disease after diagnosis, and to assess the response to patients to treatments. The reduction in new gadolinium-enhancing lesions was used as a clinical endpoint to evaluate the effectiveness of interferon-tau in treating the enrolled

multiple sclerosis patients. The MRI scans were read by expert MRI readers who manually established the location of the lesions. The number of new gadolinium-enhancing lesions was established by comparing the location of lesions on subsequent scans to the pretreatment scans.

12. The attached table summarizes the blood interleukin-10 and interferon-gamma levels and the number of new gadolinium-enhancing lesions for the sixteen patients that remained in the study at the six month time point.

13. During the first three months of treatment, the average serum IFN-γ concentrations decreased from 4.31 pg/mL to 3.93 pg/mL.

14. The average number of new gadolinium-enhancing lesions during the screening period (months -3, -2, and -1, prior to treatment) for the patients was 2.59. After six months of treatment, the average number of new gadolinium-enhancing lesions decreased to 1.31, a 61% decrease from the baseline, screening number of lesions.

15. The reduction in the number of new gadolinium-enhancing lesions, concomitant with an increase in IL-10 serum concentration, is an indicator of efficacy. It is expected that a reduction in brain lesions will be associated with a reduction in the clinical relapses, brain atrophy, and progressive disability which is expected to occur in multiple sclerosis patients.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the Unites States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: 7/20/2007

Chih-Ping Liu, Ph.D

Serum Cytokine Levels and number of new gadolinium-enhancing lesions in Multiple Sclerosis (MS) patients before and after treatment with orally-administered interferon-tau

	Screen	Treatment Period			
	Months -3 to -1	Months 1 to 3		Months 4 to 6	
	Mean	Mean	Percent Change*	Mean	Percent Change*
Number of MS Patients	16	16	16	15	15
Serum IL-10 (pg/mL)	6.44	6.72	31.53%	6.15	53.61%
Serum IFN-gamma (pg/mL)	4.31	3.93	2.54%	4.53	9.15%
Ratio IL-10/IFN-gamma	1.65	1.98	71.41%	1.70	194.32%
No. of new Gd-enhancing lesions	2.59	0.95	-63.49%	1.31	-61.22%

*Percent Change is the change from Screen for each individual patient averaged over all patients. The Percent Change for Ratio IL-10/IFN-gamma is the ratio of the percent change for serum IL-10 and serum IFN-gamma for each individual patient averaged over all patients. Expressed as a simple Percent Change from Screen averaged over all patients, the Percent Change for the Ratio IL-10/IFNg is 41.98% and 37.01% for Months 1 to 3 and Months 4 to 6, respectively.

06/663,672	SYNERGISTIC EFFECT OF CHEMOTHERAPEUTIC AGENTS ON BETA-INTERFERON	07-10-2007::13:54:36

Bibliographic Data

Application Number:	06/663,672	Customer Number:	-
Filing or 371 (c) Date:	10-22-1984	Status:	Patented Case
Application Type:	Utility	Status Date:	12-04-1985
Examiner Name:	GRON, TEDDY S	Location:	FILE REPOSITORY (FRANCONIA)
Group Art Unit:	2203	Location Date:	05-28-1999
Confirmation Number:	2070	Earliest Publication No:	-
Attorney Docket Number:	2189	Earliest Publication Date:	-
Class / Subclass:	424/008	Patent Number:	H000,022
First Named Inventor:	ABLA A. CREASEY , PIEDMONT, CA (US)	Issue Date of Patent:	02-04-1986

Title of Invention:	SYNERGISTIC EFFECT OF CHEMOTHERAPEUTIC AGENTS ON BETA-INTERFERON

Close Window